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Title: Are early-life antecedents of suicide mortality associated psychiatric disorders and suicidal ideation in midlife?

Authors: Marie-Claude Geoffroy¹, David Gunnell², Charlotte Clark³ and Christine Power⁴

¹ McGill Group for Suicide Studies
Douglas Mental Health University Institute
6875 LaSalle Boulevard
Montreal, Canada
H4H 1R3

² Department of Population Health Sciences and National Institute of Health Research Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol
University of Bristol
39 Whatley Road
Bristol, UK
BS8 2PS

³ Wolfson Institute of Preventive Medicine
Queen Mary University of London
Charterhouse Square
London, UK
EC1M 6BQ

⁴ Population, Policy and Practice
UCL Great Ormond Street Institute of Child Health
30 Guilford Street
London, UK
WC1N 1EH

Corresponding Author:

Professor Marie-Claude Geoffroy
marie-claude.geoffroy@mcgill.ca
514-761-6131 ext. 4524
McGill Group for Suicide Studies
Douglas Mental Health University Institute
Frank B. Common Pavilion
6875 LaSalle Boulevard
Montreal, Canada
H4H 1R3

Abstract

Objective: To establish whether previously identified early-life antecedents of suicide mortality (i.e. low birth-weight, younger maternal age, higher birth order, externalizing problems and adversities) are associated with proximal psychiatric disorders and suicidal ideation which are themselves associated with an increased risk of suicide.

Methods: Participants were from the 1958 British Birth Cohort (N=8905) with information on prenatal/childhood experiences and the Clinical Interview Schedule-Revised at age 45 years. Outcomes were: any internalizing disorder (anxiety disorder/depressive episode), depressive episode, alcohol use disorder and suicidal ideation.

Results: After adjustment, higher birth order ($p_{\text{trend}}=0.043$), younger maternal age ($p_{\text{trend}}=0.017$) and increased number of childhood adversities ($p_{\text{trend}}=0.026$) were associated with an increased risk of internalizing disorders. For example, the OR (95% CI) in fourth or later-born children was 1.48 (1.06-2.07) and for young maternal age (<19 years) was 1.31 (0.89-1.91). Effect sizes were similar in magnitude for depressive episode and suicidal ideation, although associations did not reach conventional significance levels. No associations were found for low birth-weight and externalizing problems (in males) and investigated outcomes.

Conclusion: Associations for younger maternal age, higher birth order and adversities with adult internalizing disorders suggest that psychiatric disorders may be on the pathway linking some early-life factors and suicide.

Keywords: Epidemiology, suicide, psychopathology, risk factors

Significant Outcomes: This large prospective birth cohort previously identified 5 early-life (up to age 7 years) risk factors for suicide mortality in adulthood: low-birth-weight, higher birth order, younger maternal age, externalizing problems in males and childhood adversities.

Using logistic regression, this 45-year longitudinal study tested whether these 5 early-life factors were independently associated with psychiatric disorders, namely any internalizing disorder (anxiety disorders/depressive episode), depressive episode alone, alcohol use disorders and suicidal ideation, that confer a high risk for suicide mortality.

Higher birth order, younger maternal age and childhood adversities were associated with internalizing disorders (including depressive episode) and suicidal ideation (trend association) in midlife, suggesting that psychiatric disorders may be on the pathway linking some early-life factors with suicide mortality.

While low-birth-weight and externalizing problems in males predicted suicide, no associations were found for our investigated outcomes, suggesting that other mechanisms are involved.

Limitations:

Associations between early-life factors and psychiatric disorders and suicidal ideation may have been underestimated as attrition was greatest among the most vulnerable individuals.

While psychiatric disorders closely related to suicide were investigated in our study, other disorders also associated with suicide mortality, namely bipolar and psychotic disorders were not investigated.

More studies are needed to better understand the complex relations with early-life factors, psychiatric outcomes and suicide mortality.

Introduction

Suicide is a major, potentially preventable, public health problem resulting in approximately 800,000 deaths each year throughout the world (1). A key focus of many suicide intervention strategies is to identify (and help) individuals who are seriously contemplating suicide or those made vulnerable by mental illness (such as depression or alcohol misuse) as these are important predictors of risk (2). While recognizing the importance of factors operating in the days/weeks prior to suicide, such as unemployment or relationship breakdown, there is an emerging body of research suggesting that early-life events occurring before/around the time of birth or in the first years of life can play a role in influencing later susceptibility to suicide (3). This line of research can be considered in the context of a developmental origins of adult disease approach, which recognizes both fetal and early childhood influences as having long-term effects on a range of adult conditions, including mental illness and suicide (4, 5).

In a previous study based on the 1958 British birth cohort, we identified five prenatal and childhood factors associated with elevated risk of suicide mortality in adulthood, from age 18 to 49 years. These early-life risk factors were low birth weight, higher birth order, younger maternal age, externalizing problems (in males) and childhood adversities such as parental death and peer bullying (6). Whilst our study (6) and several others (7-12) suggest that early-life factors may predispose to suicide, the mechanisms involved remain unknown.

Insights into the mechanisms underlying the association of early-life factors with later risk of suicide might be gained by establishing whether these specific factors are also linked to proximal psychiatric disorders (namely internalizing disorders, including depressive episode, and alcohol use disorder) and suicidal ideation that confer the highest risk for suicide(1). Very few studies have examined

associations of early-life factors with both suicide and psychiatric disorders and/or ideation/attempt (12, 13), and those that are available are based on psychiatric admission.

Aims of the study

The present study aimed to establish whether the early-life risk factors for suicide identified in our previous research (6) are also related to proximal psychiatric disorders and suicidal ideation in midlife, as these are known risk factors for suicide mortality. We focused on internalizing disorders (i.e. anxiety\depressive episode), depressive episode alone, alcohol use disorder, and suicidal ideation. We hypothesized that associations observed for early-life factors and suicide mortality would be evident for the same early-life factors and proximal psychiatric disorders and suicidal ideation.

Materials and methods

Participants

Data for this study were collected for the 1958 British Birth Cohort, an ongoing prospective study of all live births in England, Scotland and Wales in 1958 (one week in March; n=17,638, and 920 immigrants); representing 98% of all births in Britain; a detailed description is provided elsewhere (14). We use data from the birth survey (Perinatal Mortality Study), the childhood contact at 7 years and from an adult follow-up at age 45 years (in 2002-2004). All together 9,377 persons participated at age 45 from a target of 11,971 invited, and 9,263 participants completed both the mental health interview and the alcohol use questionnaire. After excluding participants who were not included in our previous analyses of suicide mortality (because they had been enrolled after age 7 years, N=358), the maximum available sample for our main analyses was 8905. Written informed consent was obtained for the clinical interview at age 45. Ethical approval was given by the South East Multi-Centre Research Ethics Committee.

Measures

Psychiatric disorders: The three psychiatric outcomes, assessed at age 45, were any internalizing disorders (i.e. any anxiety/depressive episode), depressive episode (a subset of those with internalising disorders) and alcohol use disorder. Anxiety and depressive disorders (past week) were assessed with the revised Clinical Interview Schedule (CIS-R) administered by a trained nurse in the participant's home (15, 16). We used ICD-10 diagnoses for any depressive disorders (mild, moderate, and severe) and any anxiety disorders including generalized anxiety disorder, agoraphobia, social phobia and panic disorder. Alcohol use disorder (past year) were assessed using the Alcohol Use Disorders Identification Test-AUDIT (17), a self-complete computer assisted questionnaire. It includes 10 questions assessing hazardous, and harmful drinking and alcohol dependence. Different cut-off points have been proposed for different populations (e.g. 8 in primary care (17); 11 in a general population of unemployed individuals (18)). Accordingly, in our general population-based cohort study, we used a cut-off of 11 or above to identify alcohol use disorder.

Suicidal ideation: Participants who reported having a spell of feeling sad, miserable or depressed or not being able to enjoy or take an interest in things as much as usual and felt that life isn't worth living, were asked "in the past week, have you thought of killing yourself?" While suicidal ideation was part of the criteria to define depression, suicidal ideation alone does not justify a diagnosis of depression. Only a minority (3.4%) of depressed participants reported suicidal ideation. Therefore, suicidal ideation was investigated as a separate category to provide specificity.

Early-life factors: Prenatal and childhood antecedents of suicide are identified from our previous study with the 1958 British Birth Cohort as risk factors associated with suicide deaths by 49 years ($p \leq .10$) in multivariable analyses (Appendix Table) (6). Prenatal risk factors include low birthweight (low: $< 2.5\text{kg}$ vs normal: $\geq 2.5\text{kg}$, recorded at birth by the midwife); child's birth order (reported by mothers when their child was 7 years, including all live and still births and deaths by 7 years; coded 1, 2, 3 or ≥ 4),

and maternal age at the time of the study member's birth (categorized ≤ 19 , 20-29 and > 29 years). Externalizing problems were rated by mothers when participants were 7 years old using the Rutter Behaviour Scale (19) (assessed with 4 items: destructive, irritable, disobedience and fighting rated on a 3-point scale (0=no problem, 1=intermediate, 2=problem); scores approximating the top 13% were defined as a problem, the lowest 50% were not problem behaviour, and the remainder were intermediate); as described previously (6), a childhood adversities scale by age 7 years was derived by summing 7 items (parental death, divorce/separation, domestic tension, child's contact with social services, institutional care, child's neglected appearance, and frequent peer bullying); scores were categorized as 0, 1, 2 or ≥ 3 . Additionally, father's social class in 1958 (using the 1951 Registrar General's Classification) was included as a covariate.

Statistical Analyses

Initially, we tested associations between each early-life factor and the four adult outcomes, namely any internalizing diagnoses (i.e. anxiety/depressive disorders), depressive episode only, alcohol use disorder and suicidal ideation, using logistic regression with adjustment for sex. Interactions between sex and each risk factor were included to test whether associations differed by sex. P-values for sex interaction were > 0.05 except for externalizing problems and alcohol use disorder. Thus, further analyses were combined for both sexes, except where the association was found to differ. Then, we performed analyses to assess whether the five early-life factors were independently associated with the three mid-adult psychiatric outcomes and suicidal ideation by mutually adjusting for each risk factor (i.e. low birth-weight, maternal age, birth order, externalizing problems, and adversities), and additionally adjusting for sex and father's social class. We also tested for statistical significance of trends for maternal age, birth order, externalizing problems and adversities and adult outcomes. This was done by entering those ordinal variables as continuous variables into the regression models. In additional analyses we tested p -trend for early-life factors as continuous variables (e.g. using the

externalizing problems scale ranging from 0 to 8): *p*-trend for associations with later psychiatric disorders and suicidal ideation were broadly comparable to those observed for ordinal variables entered as continuous variables (the latter are presented here). Missing data on exposures varied between 0.7% (father's social class) to 10.8% (adversities). To minimize further data loss, we imputed missing information on exposures using multiple imputations by chained equations method (20), and conducted analyses across the 10 imputed data sets (n=8905). Results based on multiple imputations were comparable to those based on complete cases, presented in supplementary table 1. As a sensitivity analysis, we also applied inverse probability weighting on the unimputed sample to allow for potential selection bias that could arise from sample attrition to age 45 years. These analyses were conducted for the sample of survivors residing in the UK in 2002/2004 when the adult psychiatric assessment took place (n=15,318). The probability of being in the study sample was estimated from logistic regressions using factors associated with attrition including sex, social class at birth, mathematics scores, internalizing and externalizing behavior problems at 7 years. The pattern of results based on inverse probability weighting was generally similar to those obtained using multiple imputation and complete cases. We present results based on multiple imputation (see supplementary online table 2 for results based on inverse probably weighting). We also undertook sensitivity analyses using an alternative cut-off for alcohol disorder (i.e. top 5%, audit scores \geq 14); results were similar to those presented here, including the differential association with externalizing problems for females versus males. Statistical analyses were performed with SPSS 23 software.

Results

At age 45 years, alcohol use disorder was the most prevalent disorder (10.8%), whilst 6.0% of the sample had any psychiatric diagnosis; including 2.0% with a diagnosis of depression; fewer participants (0.5%) reported suicidal ideation in the past week (**Table 1**). The prevalence of any

internalizing disorders and depressive episode was higher in females than males, while the prevalence of alcohol use disorder was higher in males.

Table 2 shows prevalence of each of the psychiatric disorders and suicidal ideation for the five early-life factors, while ORs and 95% CI adjusted for sex only, and mutually adjusted for each other, sex and father's social class at birth are reported in **Table 3**. Considering the broadest category of any internalizing disorders (i.e. anxiety/depressive episode) as the outcome, associations were observed for birth order, maternal age and adversities. There was a trend of increasing risk of any internalizing disorders with increasing birth order ($p_{\text{trend}}=.043$), from the first born (reference) to fourth born or later births (OR:1.48, 1.06,2.07). For maternal age, a trend ($p_{\text{trend}}=.019$) was observed indicating that offspring of younger mothers were at the highest risk of any internalizing disorders. For childhood adversities, offspring exposed to the higher levels of adversity were at increased risk of any internalizing disorders in mid-life($p_{\text{trend}}=.026$).

For depressive episode alone and suicidal ideation trends for birth order, maternal age and number of childhood adversities were similar to those observed for any internalizing disorders. However, as expected given small *ns* for these outcomes, 95% confidence intervals for all associations included 1 and none of the tests for trend reached conventional levels of significance ($p>0.05$).

The only early-life factor associated with adult alcohol use disorder was externalizing problems; this association was seen in females, but not in males (p interaction = 0.031). There was no clear evidence of an association of low birth weight with any of the disorders investigated. We conducted sensitivity analyses to examine whether early-life factors were also associated with non-depression internalizing disorders, namely anxiety disorders (e.g. generalized anxiety, agoraphobia, social phobia and panic). As shown in Supplementary Table 3, we found associations with birth order ($p=.002$), maternal age ($p=.009$) and adverse emotional experiences ($p=.004$) that were similar to those found for depressive episode.

Discussion

Using a large prospective British birth cohort, we found consistent associations whereby higher birth order, younger maternal age, and increased number of adverse childhood experiences were associated with any internalizing disorders (i.e. anxiety/depressive disorders) at 45 years. Associations persisted in mutually adjusted models indicating independent effects. Effect sizes were generally of similar magnitude for depressive episode alone and suicidal ideation, although not reaching conventional levels of significance. Only externalizing disorders were associated with risk of alcohol use disorder, although this association was evident in females and not males. These findings support the argument that proximal internalizing psychiatric disorders are on the pathway linking some prenatal/childhood factors (but not all) with suicide mortality. However, low birth-weight was not related to the mid-life disorders investigated here.

Methodological considerations

While participants included in the study at age 45 years are broadly representative of the original cohort (21), attrition had occurred over time. Like other prospective studies, attrition was greatest among the most vulnerable participants, potentially resulting in underestimation of the associations between prenatal/childhood influences and our mid-life outcomes. However, findings from weighted analyses conducted to reduce such selection bias were similar to those based on complete cases suggesting that results reported here are robust. To further minimize the impact of missing data in our analyses, we used multiple imputation following current guidelines (22). While clinical diagnosis was available for anxiety and depressive disorders, alcohol use disorder was measured via self-report questionnaire. Suicidal ideation was assessed via a single question asked only to participants with depressive symptoms. Assessment of internalizing disorders and suicidal ideation was limited to the previous week, hence leading to the low prevalence of these conditions. Therefore, study power was limited for

detecting statistically significant associations with our relatively uncommon prenatal/childhood exposures and specific disorders, namely depressive episode and suicidal ideation. In particular, effect estimates for suicidal ideation whilst frequently amongst the highest observed, rarely showed confidence intervals that excluded 1. Nevertheless, this limitation also applied to our previous analyses with suicide mortality as the outcome ($n=44$ suicides) for which associations were detected. As information on psychiatric disorders and suicidal ideation was not available prior to death by suicide, it was not possible to assess the role of these possible intermediaries using conventional mediational models. While the most common forms of mental disorders related to suicide mortality are considered here, we lack information on bipolar and psychotic disorders for which the rate of suicide is also elevated (23).

Despite their limitations, prospective studies like ours with long-term follow-up and relying on clinical assessment of mental disorders, offer the best opportunity to investigate associations of early-life suicide antecedents with later psychiatric disorders and suicidal ideation that confer a heightened risk for suicide. These associations were investigated in a large population-based cohort, the same cohort that was used to identify prenatal/childhood antecedents of suicide mortality, thereby facilitating direct comparisons of magnitude of associations.

Interpretation of the findings

Our previous research reported associations between five prenatal/childhood factors and suicide mortality (6). However, it was unknown whether the same factors were also related to proximal psychiatric disorders for suicide mortality. It is possible, for example, that early-life risk factors may influence other potential pathways influencing suicide risk such as impulsiveness or help-seeking behaviours. To the best of our knowledge, our study is the first to assess life-course associations between previously identified prenatal and childhood antecedents of suicide and psychiatric outcomes clinically assessed in the general population. Our findings for three prenatal/childhood factors, namely

higher birth order, younger maternal age and number of childhood adversities and mid-adult internalizing disorders are consistent with those observed previously for suicide mortality in this population (6). However, the strength of associations linking these early-life factors with any internalizing psychiatric disorders were weaker than for suicide. For example, the adjusted hazard for suicide for people exposed to three or more adversities was 3.12 (CI 1.01,9.62), while odds ratio for any internalizing disorders was 1.50 (CI 0.72, 3.16). It is possible that the weaker associations shown here may in part reflect gender differences in the prevalence of mental disorders (female predominance) versus suicide (male predominance). Only a handful of studies have examined associations of early-life factors with both suicide and psychiatric disorders simultaneously and they have done so using hospital admission for psychiatric illness as an indicator of mental health. Hospital admission is likely to reflect extreme mental health problems and may be influenced by an array of contextual factors influencing the likelihood of admission in someone experiencing mental illness, e.g. proximity to hospital/availability of support. Riordan & colleagues (12) reported that younger maternal age and higher parity were similarly associated with suicide mortality, psychiatric admission and self-harm, while low birth-weight was associated with psychiatric admission, but not suicide mortality. In Lahti & colleagues (13) late preterm (a proxy for low birth-weight) was associated with suicide in males, but not with severe psychiatric disorders requiring hospitalization or contributing to death. In our current research, low birth-weight was not associated with any of the psychiatric disorders investigated. While early life externalizing problems strongly predicted suicide mortality in males (HR: 2.96), no association was found for males with our psychiatric outcomes and suicidal ideation, suggesting that other underlying mechanisms might be involved, such as irritability/impulsivity(24).

It is still not clear how early-life experiences could translate into mental illnesses and suicidal risks, in adult life, several years after the traumatic exposure. It is possible that early-life events can produce

changes in DNA methylation that subsequently influence an individual vulnerability to mental disorders and suicide. DNA methylation is one of several epigenetic mechanisms known to be influenced by the external environment, and in turn affects transcriptional regulation and gene expression (25, 26).

In sum, our findings contribute to the evidence-base by suggesting that adult internalizing disorders may be on the pathway linking some though not all early-life factors with suicide mortality. More studies are needed to draw firmer conclusions about the underlying pathways linking early-life factors with suicide mortality. To improve intervention for high-risk individuals we need to better understand the complex relations with prenatal and childhood suicide risks and intermediary psychiatric outcomes.

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References

1. World Health Organization. Preventing suicide: A global imperative: World Health Organization; 2014.
2. Turecki G, Brent DA. Suicide and suicidal behaviour. *The Lancet*. 2016;387(10024): 1227-39.
3. Gunnell D, Lewis G. Studying suicide from the life course perspective: implications for prevention. *Br J Psychiatry*. 2005;187(3):206-8.
4. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61-73.
5. Kim DR, Bale TL, Epperson CN. Prenatal programming of mental illness: current understanding of relationship and mechanisms. *Current psychiatry reports*. 2015;17(2):1-9.
6. Geoffroy MC, Gunnell D, Power C. Prenatal and childhood antecedents of suicide: 50-year follow-up of the 1958 British Birth Cohort study. *Psychol Med*. 2014;44(6):1245-56.
7. Bjørngaard JH, Bjerkeset O, Vatten L, Janszky I, Gunnell D, Romundstad P. Maternal age at child birth, birth order, and suicide at a young age: a sibling comparison. *Am J Epidemiol*. 2013;177(7):638-44.
8. Alaräisänen A, Miettunen J, Pouta A, Isohanni M, Räsänen P, Mäki P. Ante- and perinatal circumstances and risk of attempted suicides and suicides in offspring: the Northern Finland birth cohort 1966 study. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47(11):1783-94.
9. Mittendorfer-Rutz E, Rasmussen F, Wasserman D. Restricted fetal growth and adverse maternal psychosocial and socioeconomic conditions as risk factors for suicidal behaviour of offspring: a cohort study. *Lancet*. 2004;364(9440):1135-40.
10. Guldin M-B, Li J, Pedersen HS, Obel C, Agerbo E, Gissler M, et al. Incidence of Suicide Among Persons Who Had a Parent Who Died During Their Childhood: A Population-Based Cohort Study. *JAMA psychiatry*. 2015;72(12):1227-34.
11. Niederkrotenthaler T, Rasmussen F, Mittendorfer-Rutz E. Perinatal conditions and parental age at birth as risk markers for subsequent suicide attempt and suicide: a population based case-control study. *Eur J Epidemiol*. 2012;27(9):729-38.
12. Riordan D, Morris C, Hattie J, Stark C. Family size and perinatal circumstances, as mental health risk factors in a Scottish birth cohort. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47(6):975-83.

13. Lahti M, Eriksson J, Heinonen K, Kajantie E, Lahti J, Wahlbeck K, et al. Late preterm birth, post-term birth, and abnormal fetal growth as risk factors for severe mental disorders from early to late adulthood. *Psychological medicine*. 2015;45(05):985-99.
14. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). *Int J Epidemiol*. 2006;35(1):34-41.
15. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological Medicine*. 1992;22(02):465-86.
16. Clark C, Rodgers B, Caldwell T, Power C, Stansfeld S. Childhood and adulthood psychological ill health as predictors of midlife affective and anxiety disorders: the 1958 British Birth Cohort. *Arch Gen Psychiatry*. 2007;64(6):668-78.
17. Saunders JB, Aasland OG, Babor TF, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption - II. *Addiction*. 1993;88(6):791-804.
18. Claussen B, Aasland OG. The Alcohol Use Disorders Identification Test (AUDIT) in a routine health examination of long - term unemployed. *Addiction*. 1993;88(3):363-8.
19. Elander J, Rutter M. Use and development of the Rutter parents' and teachers' scales. *Int J Methods Psychiatr Res*. 1996;6(2):63-78.
20. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res*. 2011;20(1):40-9.
21. Atherton K, Fuller E, Shepherd P, Strachan DP, Power C. Loss and representativeness in a biomedical survey at age 45 years: 1958 British birth cohort. *J Epidemiol Community Health*. 2008;62(3):216-23.
22. Sterne JAC, Cox DR, Smith GD. Sifting the evidence—what's wrong with significance tests? Another comment on the role of statistical methods. *BMJ*. 2001;322(7280):226-31.
23. Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry*. 1997;170(3):205-28.
24. Turecki G. Dissecting the suicide phenotype: the role of impulsive-aggressive behaviours. *J Psychiatry Neurosci*. 2005;30(6):398-408.
25. Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N. The neurodevelopmental origins of suicidal behavior. *Trends Neurosci*. 2012;35(1):14-23.
26. Turecki G, Meaney MJ. Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. *Biol Psychiatry*. 2014.

Appendix table: Sex and fully adjusted associations of early-life antecedents of suicide by 49 years; hazard ratio (HR) and 95% confidence intervals (CI); $n=12\ 399$ with 44 suicides.

	Suicide mortality	
	Sex adjusted	Fully adjusted ¥
Low birth weight		
Normal: ≥ 2.5 kg	ref.	ref.
Low: < 2.5 kg	2.94 (1.24,6.96)	2.48 (1.03,5.95)
Child's birth order		
1	ref.	ref.
2	1.19 (0.55,2.56)	1.38 (0.62,3.06)
3	1.49 (0.62,3.60)	1.84 (0.73,4.68)
≥ 4	1.75 (0.77,3.98)	2.27 (0.90,5.75)
p for trend	.157	.063
Mother's age at child's birth		
≤ 19 years	1.12 (0.34,3.66)	1.18 (0.34,4.13)
20-29 years	ref.	ref.
> 29 years	0.51 (0.24,1.06)	0.41 (0.19,0.91)
p for trend	.071	.034
Externalizing behaviour		
No problem	ref.	ref. \pm
Intermediate	1.78 (0.82,3.87)	1.59 (0.73,3.47)
Problem	2.73 (1.16,6.42)	1.76 (0.73,4.24)
p for trend	.020	.199
No. of emotional adverse experiences		
0	ref.	ref.
1	2.06 (0.97,4.38)	1.53 (0.70,3.34)
2	3.11 (1.09,8.89)	2.21 (0.75,6.54)
≥ 3	5.85 (2.05,16.72)	3.12 (1.01,9.62)
p for trend	$\leq .001$.033

Adapted from Geoffroy et al. (2014). Psychol Med.

¥ Mutually adjusted for all early-life factors, sex, father's social class, dry during day after age 3 years, internalizing and externalizing behaviours (teacher reports).

\pm The elevated suicide mortality risk associated with externalizing behaviors was seen in males (HRS=2.43, 95% CI 0.91,6.48 for intermediate and 2.96. 95% CI 1.03,8.47 for

problems, $p_{\text{trend}}=0.050$), but not in females (HR=0.47, 95% CI 0.80,2.75 for intermediate and N.A. for problems).

Table 1: Descriptive statistics for psychiatric disorders and suicidal ideation at age 45 years, %(n); n=8905

	Overall	Males	Females	P-values for sex differences
Any internalizing diagnoses‡	6.0(530)	4.7(209)	7.2(321)	≤.001
Depressive episode	2.0(177)	1.4(64)	2.5(113)	≤.001
Alcohol use disorder	10.8(961)	16.1(709)	5.6(252)	≤.001
Suicidal ideation (past week)	0.6(51)	0.5(20)	0.7(31)	.160

‡ includes depressive episode, generalized anxiety disorder (3.9%, n=343), agoraphobia (0.5%, n=41), social phobia (0.3%, n=31), panic disorder (0.2%;n=19).

Table 2: Descriptive statistics for psychiatric disorders and suicidal ideation at age 45 years by early-life antecedents of suicide, %(n); n=8905‡

	Any internalizing diagnoses§		Depressive episode		Alcohol use disorder		Suicidal ideation	
	Yes %(n)	No %(n)	Yes %(n)	No %(n)	Yes %(n)	No %(n)	Yes %(n)	No %(n)
Low birth weight								
Normal: ≥2.5 kg	5.9(471)	94.1(7554)	2.0(159)	98.0(7866)	10.8(865)	89.2(7160)	0.5(44)	99.5(7981)
Low: <2.5 kg	7.2(33)	92.8(428)	2.4(11)	97.6(450)	10.8(50)	89.2(411)	0.9(4)	99.1(457)
Child's birth order								
1	5.3(163)	94.7(2897)	1.9(58)	98.1(3002)	9.8(299)	90.2(2761)	0.4(12)	99.6(3048)
2	6.0(151)	94.0(2356)	2.0(51)	98.0(2456)	10.5(264)	89.5(2443)	0.8(20)	99.2(2487)
3	5.8(72)	94.2(1172)	1.4(18)	98.6(1226)	11.7(146)	88.3(1098)	0.7(9)	99.3(1235)
≥4	7.5(87)	92.5(1076)	3.0(35)	97.0(1128)	11.8(137)	88.2(1026)	0.4(5)	99.6(1158)
Mother's age at child's birth								
≤19 years	8.0(35)	92.0(405)	3.0(13)	97.0(427)	9.3(41)	90.7(399)	0.9(4)	99.1(436)
20-29 years	6.1(330)	93.9(5089)	2.0(109)	98.0(5310)	10.7(582)	89.3(4837)	0.6(34)	99.4(5385)
>29 years	5.3(154)	94.7(2756)	1.8(52)	98.2(2858)	11.2(325)	88.8(2885)	0.4(12)	99.6(2898)
Externalizing behaviour								
No problem	5.6(181)	94.4(3060)	1.9(62)	98.1(3179)	9.0(292)	91.0(2949)	0.5(15)	99.5(3226)
Intermediate	5.9(210)	94.1(3374)	2.0(71)	98.0(3513)	10.8(387)	89.2(3197)	0.5(18)	99.5(3566)
Problem	6.8(78)	93.2(1063)	2.5(28)	97.5(1113)	14.5(165)	85.5(976)	1.1(12)	98.9(1129)
No. of emotional adverse experiences								
0	5.4(363)	94.6(6298)	2.0(130)	98.0(6531)	10.5(700)	89.5(5961)	0.5(32)	99.5(6629)
1	7.6(70)	92.4(852)	1.8(17)	98.2(905)	10.1(93)	89.9(829)	0.8(7)	99.2(915)
2	10.3(24)	89.7(208)	3.4(8)	96.6(224)	13.4(31)	86.6(201)	2.2(5)	97.8(227)
≥3	9.4(12)	90.6(116)	5.5(7)	94.5(121)	10.9(14)	89.1(114)	1.6(2)	98.4(126)

‡ Frequencies are based on maximum *n* available

§ includes depressive episode, generalized anxiety disorder, agoraphobia, social phobia, panic disorder.

Table 3: Sex adjusted and fully adjusted* associations of early-life antecedents of suicide with psychiatric disorders and suicidal ideation at age 45 years; odds ratio (OR) and 95% confidence intervals (CI); n=8905

	Any internalizing diagnoses§		Depressive episode		Alcohol use disorder		Suicidal ideation	
	Sex adjusted	Fully adjusted	Sex adjusted	Fully adjusted	Sex adjusted	Fully adjusted	Sex adjusted	Fully adjusted
Low birth weight								
Normal: ≥2.5 kg	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Low: <2.5 kg	1.21(0.89,1.81)	1.21 (0.84,1.73)	1.31(0.71,2.39)	1.24 (0.67,2.30)	1.21(0.89,1.65)	1.17(0.85,1.60)	1.86(0.69,4.99)	1.67(0.62,4.52)
Child's birth order								
1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
2	1.12(0.89,1.42)	1.22 (0.95,1.55)	1.09(0.72,1.65)	1.19(0.77,1.84)	1.04(0.86,1.24)	1.03(0.85,1.23)	1.91(0.92,3.99)	2.25(1.06,4.80)
3	1.09(0.75,1.59)	1.19(0.81,1.77)	0.81(0.46,1.42)	0.87(0.49,1.54)	1.25(0.99,1.59)	1.21(0.93,1.56)	1.68(0.66,4.28)	1.95(0.72,5.28)
≥4	1.35(1.01,1.79)	1.48(1.06,2.07)	1.46(0.93,2.29)	1.57(0.93,2.66)	1.21(0.93,1.56)	1.14(0.85,1.56)	1.11(0.39,3.22)	1.26(0.40,3.99)
p for trend	.076	.043	.271	.207	.055	.209	.655	.471
Mother's age at child's birth								
≤19 years	1.38(0.97,1.97)	1.31 (0.89,1.91)	1.51(0.86,2.68)	1.40(0.77,2.54)	0.91(0.65,1.28)	0.89(0.62,1.26)	1.53(0.55,4.28)	1.59(0.54,4.75)
20-29 years	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
>29 years	0.87(0.71,1.05)	0.80 (0.64,1.01)	0.88(0.63,1.23)	0.83 (0.57,1.21)	1.06(0.91,1.23)	1.04(0.88,1.22)	0.66(0.34,1.27)	0.68(0.34,1.39)
p for trend	.020	.019	.139	.162	.325	.495	.105	.162
Externalizing behaviour								
No problem	ref.	ref.	ref.	ref.	ref.	ref.±	ref.	ref.
Intermediate	1.12(0.89,1.39)	1.09 (0.87,1.37)	1.11(0.77,1.58)	1.08(0.75,1.54)	1.07(0.89,1.29)	1.07(0.89,1.29)	1.16(0.58,2.37)	1.14(0.56,2.32)
Problem	1.29(0.98,1.70)	1.14(0.85,1.52)	1.37(0.86,2.18)	1.24(0.77,1.99)	1.43(1.13,1.82)	1.41(1.10,1.79)	2.46(1.10,5.49)	2.02(0.87,4.68)
p for trend	.070	.319	.205	.430	.006	.010	.046	.128
No. of emotional adverse experiences								
0	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
1	1.47(1.12,1.92)	1.38(1.05,1.81)	0.96(0.57,1.60)	0.86(0.51,1.44)	0.97(0.72,1.30)	0.91(0.67,1.24)	1.43(0.62,3.29)	1.27(0.55,2.94)
2	1.75(1.14,2.68)	1.56(1.01,2.41)	1.42(0.70,2.90)	1.18(0.56,2.45)	1.26(0.85,1.86)	1.17(0.80,1.71)	3.51(1.42,8.68)	3.01(1.14,7.89)
≥3	1.69(0.82,3.48)	1.50(0.72,3.16)	1.96(0.82,4.68)	1.70(0.71,4.08)	1.22(0.60,2.49)	1.11(0.55,2.24)	1.99(0.45,8.75)	1.54(0.34,7.05)
p for trend	.003	.026	.090	.304	.361	.625	.019	.103

§ includes depressive episode, generalized anxiety disorder, agoraphobia, social phobia, panic disorder.

‡ Mutually adjusted for all early-life factors, sex and father's social class

± The elevated alcohol use disorder risk associated with externalizing behaviors was seen in females (ORS= 1.33, 95% CI 0.94, 1.89 for intermediate and 2.06, 95% CI 1.36, 3.13 for problems, p -trend \leq .001), but not in males (ORS= 0.97, 95% CI 0.77, 1.21 for intermediate and 1.21, 95% CI 0.92, 1.59 for problems, p -trend=.257).

